Optimizing Care for Individuals with Type 2 Diabetes and Cardiovascular Disease: a Multidisciplinary Approach

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Goal of this talk

- Reinforce that there is an enormous opportunity to provide better care for your patients with cardiovascular disease and diabetes
- Get you more familiar with how and when to use SGLT-2i's and GLP-1 RA's
- Encourage you as primary care providers to take more ownership of diabetes treatments with CV protection

Disclosures

- Research contracts: AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Daiichi Sankyo, FDA, Janssen, Novartis, GSK, Medtronic Foundation, Pfizer, The Medicines Company, FDA, NIH
- Consulting/Honoraria: AstraZeneca, Bayer, BMS, Boston Scientific, GSK, Pfizer, Lilly, Daiichi Sankyo, Novartis, Novo Nordisk, Boehringer Ingelheim, Medtronic, Medtronic Foundation, The Medicines Company
- For full listing see w*ww.dcri.duke.edu/research/coi.jsp*

Life Expectancy Decreasing for First Time Since 1918 Flu Epidemic

The premature death rate has increased for the third straight year, along with **increases in rates of cardiovascular and drug deaths.**

PREMATURE DEATHS

+3%

Since 2015

DRUG DEATHS

+7%

In the past year

CARDIOVASCULAR DEATHS

+2%

Since 2015

Cardiovascular Risk Reduction in Diabetes

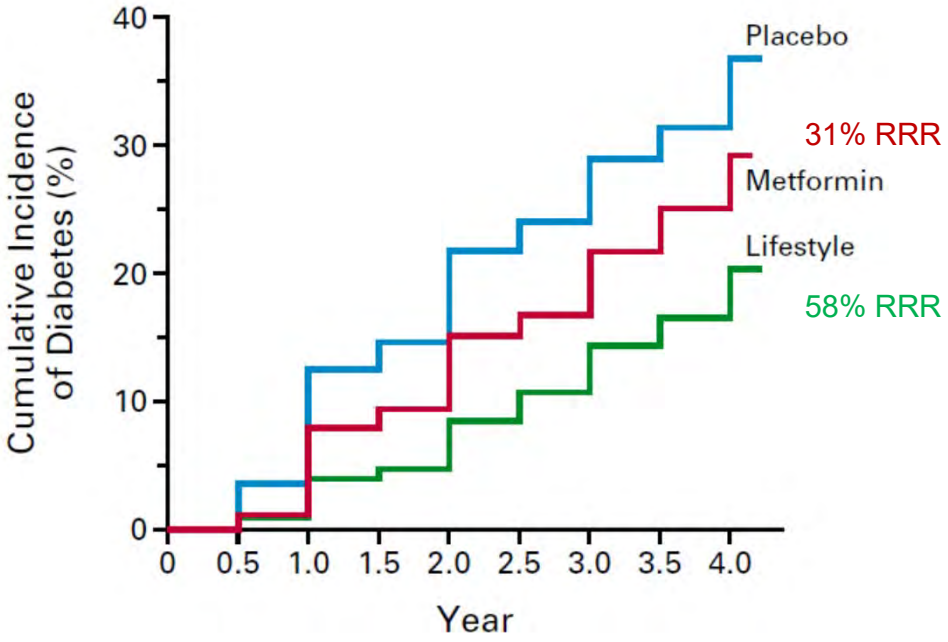
Many interventions are important and effective in reducing CV risk in patients with diabetes

Medications for T2DM and ASCVD

- Aspirin
- ACE/ARB
- High intensity statin
- SGLT-2i or GLP-1 RA

REDUCTION IN THE INCIDENCE OF TYPE 2 DIABETES WITH LIFESTYLE INTERVENTION OR METFORMIN

DIABETES PREVENTION PROGRAM RESEARCH GROUP*



- 3234 patients with prediabetes
- Lifestyle intervention of goal of 7% weight loss through diet, and 150 minutes moderate physical activity (brisk walking)

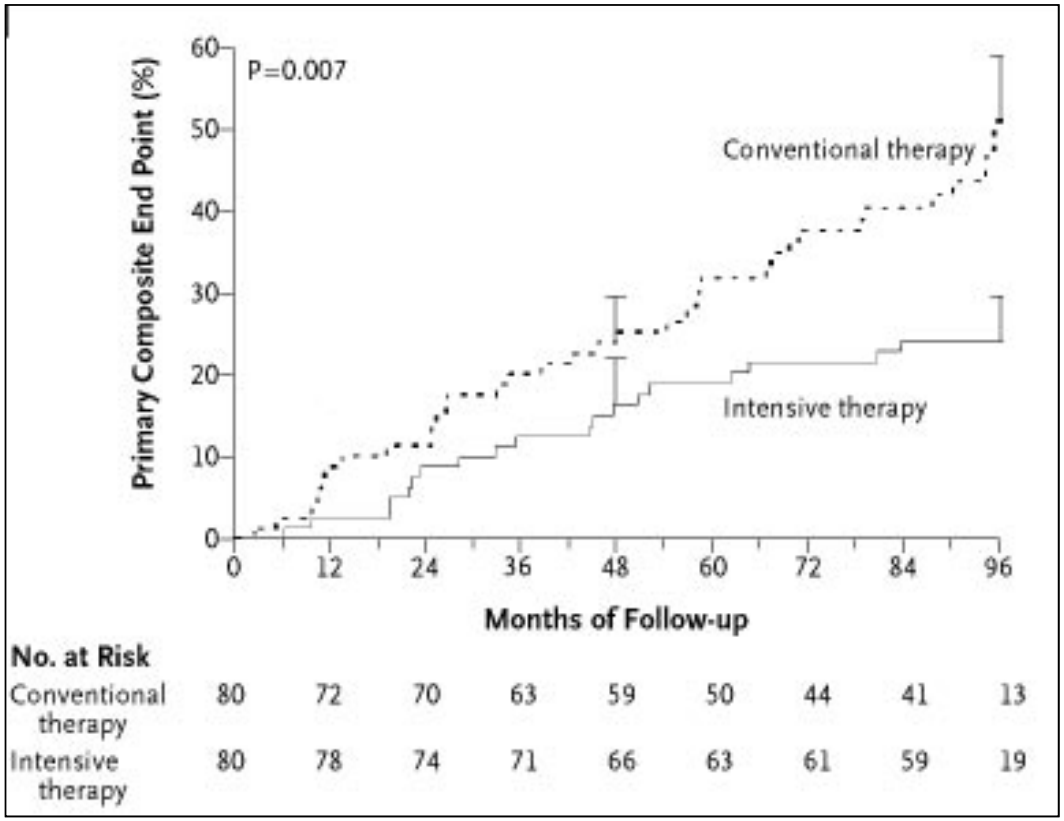
NEJM 2002;346:393-403

How are we doing managing CV risk in patients with diabetes?

Intensive Multifactorial Therapy Reduces Cardiovascular Complications in Type 2 Diabetes: Steno-2

Unadjusted HR 0.47
(95% CI 0.24-0.73)

Adjusted HR 0.47
(95% CI 0.22-0.74)



Gaede P. NEJM 2003; 348:383-93

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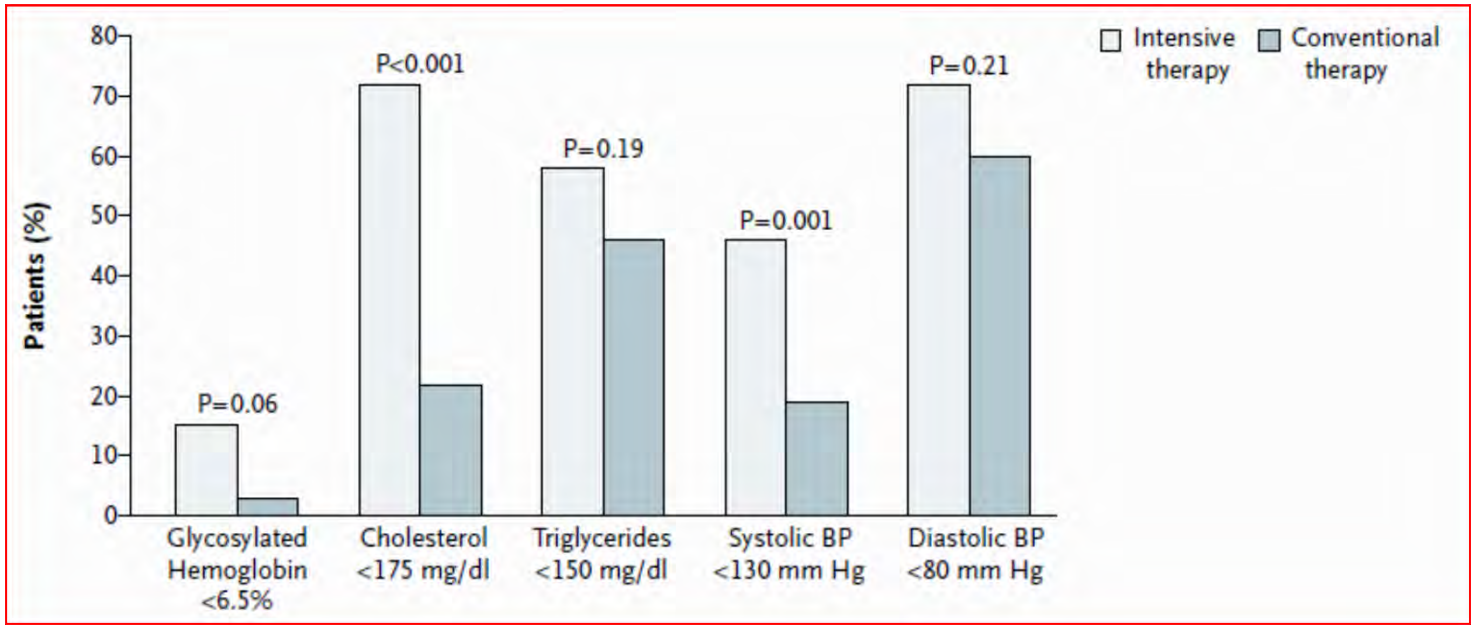
Intensive Multifactorial Therapy Reduces Cardiovascular Complications in Type 2 Diabetes



Gaede P. NEJM 2003; 348:383-93

Care Delivery Systems

- 33-49% of patients still do not meet targets for A1C, blood pressure, or lipids.
- 14% meet targets for all A1C, BP, lipids, and nonsmoking status.
- Progress in CVD risk factor control is slowing.
- Substantial system-level improvements are needed.
- Delivery system is fragmented, lacks clinical information capabilities, duplicates services & is poorly designed.

www.BetterDiabetesCare.nih.gov

American Diabetes Association Standards of Medical Care in Diabetes.
Promoting Health and Reducing Disparities in Populations. *Diabetes Care* 2017; 40 (Sup 1): S6-S10

American Diabetes Association.

Two worlds of management of CV risk in diabetes

Diabetologist

- Focus on blood sugar
- Expert in wide range of hypoglycemia medications
- Expert in care of complex diabetes, microvascular complications
- Defers to cardiologist on CV protection

Cardiologist/ Primary care

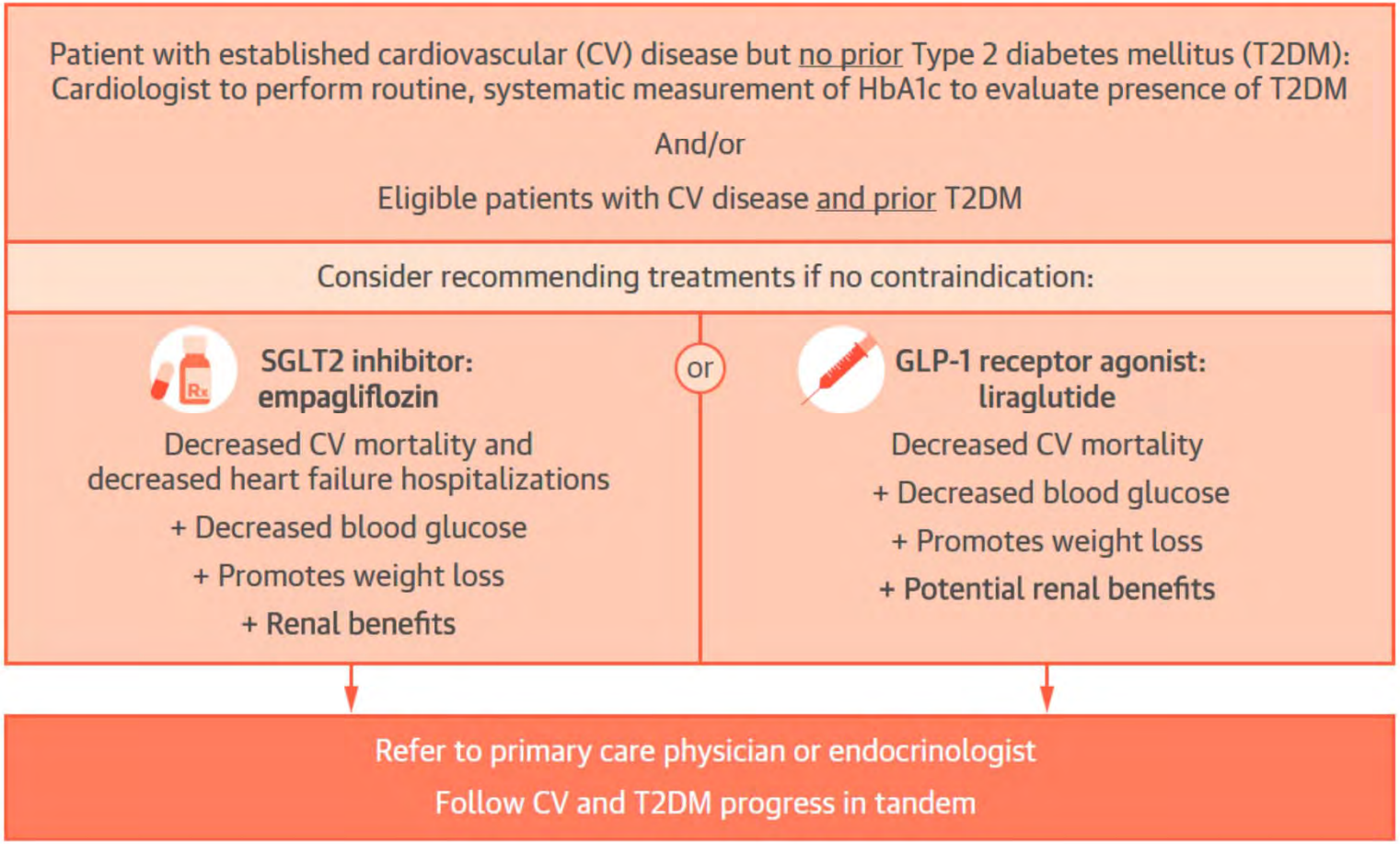
- Focus on hypertension, lipids, diet
- Management of cardiovascular disease
- Defers to diabetologist on diabetes drugs

64 yo M with prior anterior MI, LV EF 35, new HF (NYHA class II). BP 150/90. HbA1c 8.5, on metformin and pioglitizone. Creatinine clearance 45 ml/m.

What should you do as the cardiologist / primary care provider?

1. Recommend exercise, diet, control BP, recheck HbA1c in 2 months
2. Begin furosemide, ACE-I, beta blocker
3. Change pioglitizone to SGLT-2 inhibitor
4. Begin insulin
5. Refer to endocrinologist for diabetes management

Novel Paradigm for Care of CV Disease and T2DM



Sattar, N. et al. J Am Coll Cardiol. 2017;69:2646–56.

Diabetes with heart failure is common

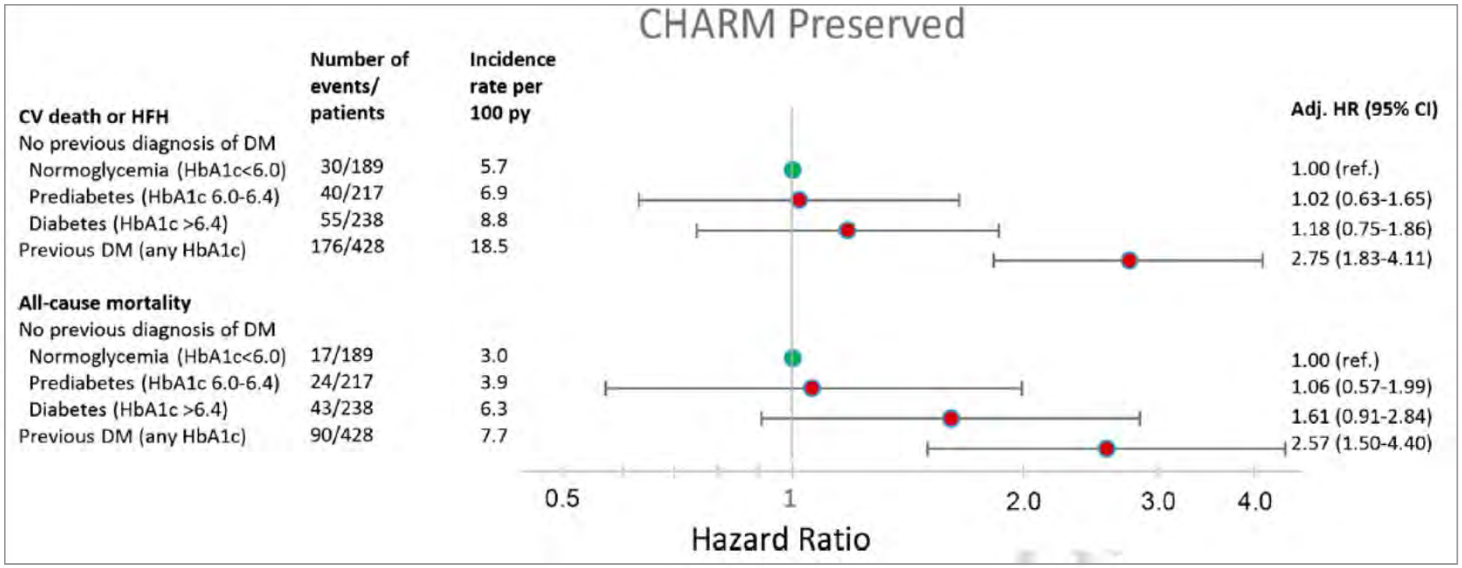
Prevalence of Prediabetes and Undiagnosed Diabetes in Patients with HFpEF and HFrEF and Associated Clinical Outcomes

Søren Lund Kristensen[1,2] · Pardeep Jhund[1] · Matthew Lee[1] · Lars Køber[2] · Scott D. Solomon[3] · Christopher B. Granger[4] · Salim Yusuf[5] · Marc A. Pfeffer[3] · Karl Swedberg[6] · John J. V. McMurray[1] · CHARM Investigators and Committees

62% had diabetes; one quarter had undiagnosed diabetes

HFrEF: 26% undiagnosed*, 36% prior, 22% pre

HFpEF: 22% undiagnosed*, 40% prior, 20% pre



*HbA1c > 6.4

Cardiovasc Drugs Ther 2017

U.S. Food and Drug Administration
Protecting and Promoting Public Health

Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

FDA NEWS RELEASE

2008

FOR IMMEDIATE RELEASE
December 17, 2008

Media Inquiries:
Karen Riley, 301-796-4674
Consumer Inquiries:
888-INFO-FDA

FDA Announces New Recommendations on Evaluating Cardiovascular Risk in Drugs Intended to Treat Type 2 Diabetes

The U.S. Food and Drug Administration recommended today that manufacturers developing new drugs and biologics for type 2 diabetes provide evidence that the therapy will not increase the risk of such cardiovascular events as a heart attack. The recommendation is part of a new guidance for industry that applies to all diabetes drugs currently under development.

"We need to better understand the safety of new antidiabetic drugs. Therefore, companies should conduct a more thorough examination of their drugs' cardiovascular risks during the product's development stage," said Mary Parks, M.D., director, Division of Metabolism and Endocrinology Products, Center for Drug Evaluation and Research (CDER), FDA. "FDA's guidance outlines the agency's recommendations for doing such an assessment."

"…sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk."

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116994.htm

Selected CVOTs in T2DM (adapted from Inzucchi SE)

Study	SAVOR	EXAMINE	TECOS	CARMELINA	CAROLINA
DPP4-i	saxagliptin	alogliptin	sitagliptin	linagliptin	linagliptin
Comparator	placebo	placebo	placebo	placebo	sulfonylurea
N	16,492	5,380	14,671	6,979	6,042
Results	2013	2013	June 2015	2018	2019

NEUTRAL NEUTRAL NEUTRAL NEUTRAL NEUTRAL

Study	ELIXA	LEADER	SUSTAIN 6	EXSCEL	HARMONY	REWIND
GLP1-RA	lixisenatide	liraglutide	semaglutide	exenatide	albiglutide	dulaglutide
Comparator	placebo	placebo	placebo	placebo	placebo	placebo
N	6,068	9,340	3,297	14,752	9,463	9,901
Results	2015	2016	2016	2017	2018	2019

NEUTRAL WOW!!! POS NEUTRAL + POS POS

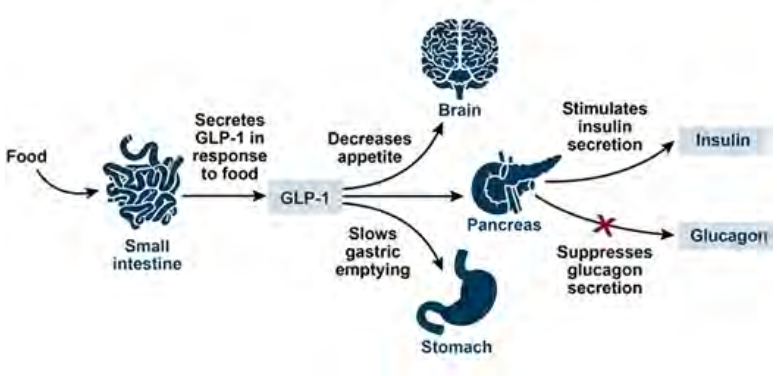
Study	EMPA-REG	CANVAS	DECLARE	VERTIS CV
SGLT-2-i	empagliflozin	canagliflozin	dapagliflozin	ertugliflozin
Comparator	placebo	placebo	placebo	placebo
N	7,020	10,142	22,200	8,000
Results	Sept 2015	2017 ADA	2019	2020

WOW!!! POS POS

2019 Updates for Cardiologists/ Primary Care Providers

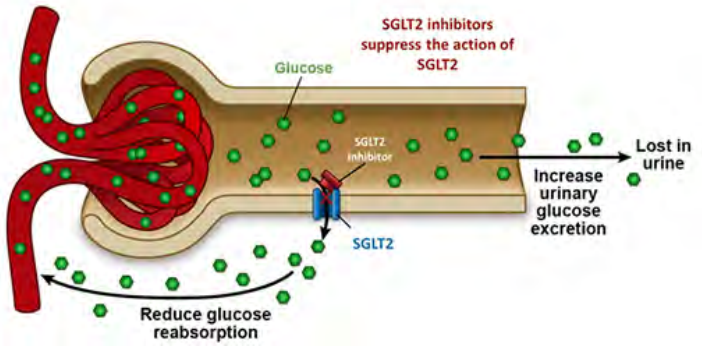
1. Evidence that SGLT-2 inhibitors are even more clearly "cardiovascular drugs" as they provide benefit regardless of diabetes
2. Progress on development of oral GLP1 RA that appears effective and safe (but CV outcome trials pending)

GLP-1 receptor agonists



Meier JJ et al. Nat Rev Endocrinol. 2012

SGLT-2 inhibitors

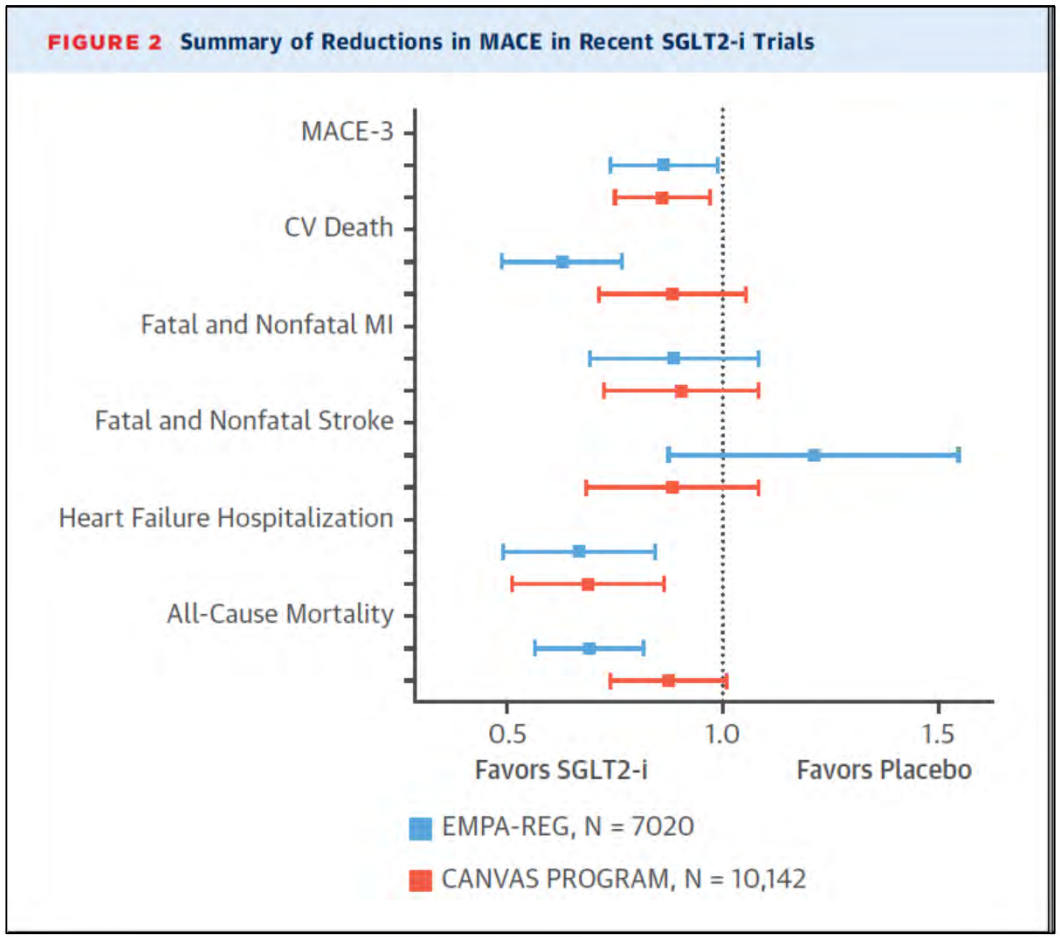


Wright EM et al. Physiol Rev 2011

MACE	**14% RRR**	**13% RRR**
HF hosp	**7% RRR**	**31% RRR**
Renal	**8% RRR**	**45% RRR**

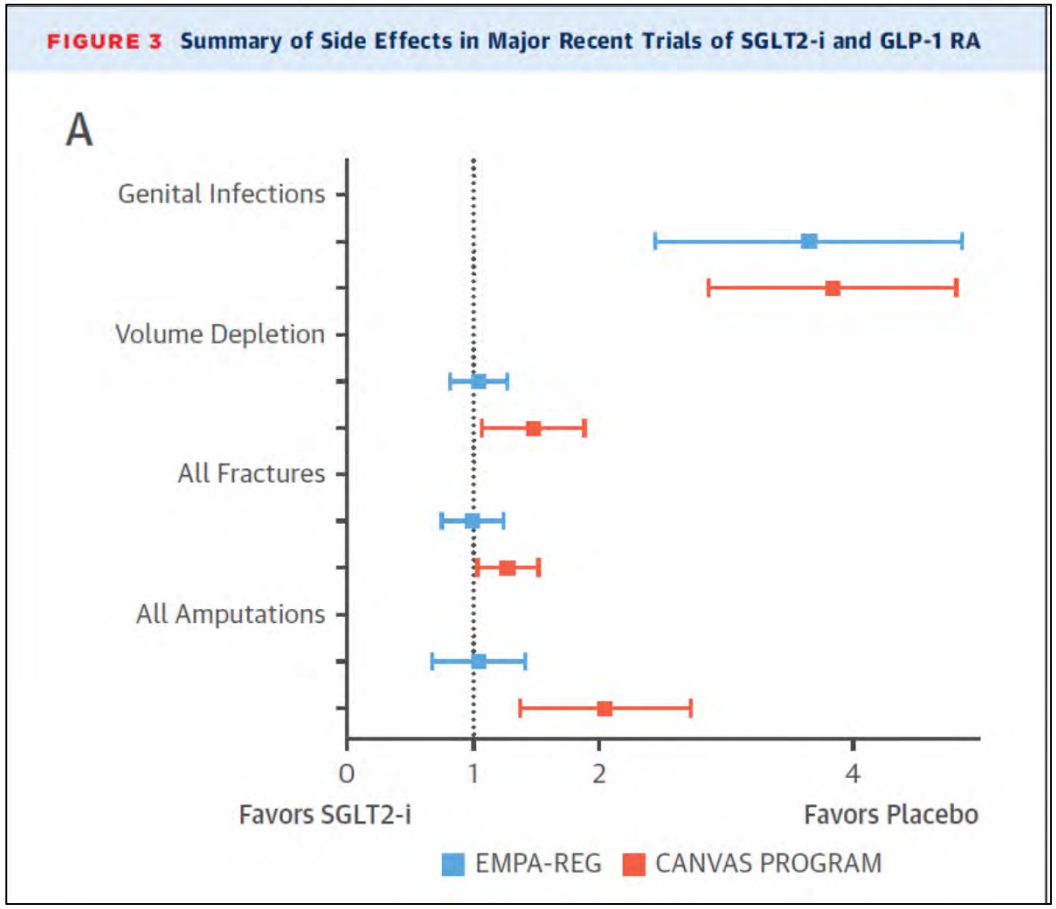
Zelniker et al. Lancet 2019

Improved CV outcome with SGLT2 inhibitors



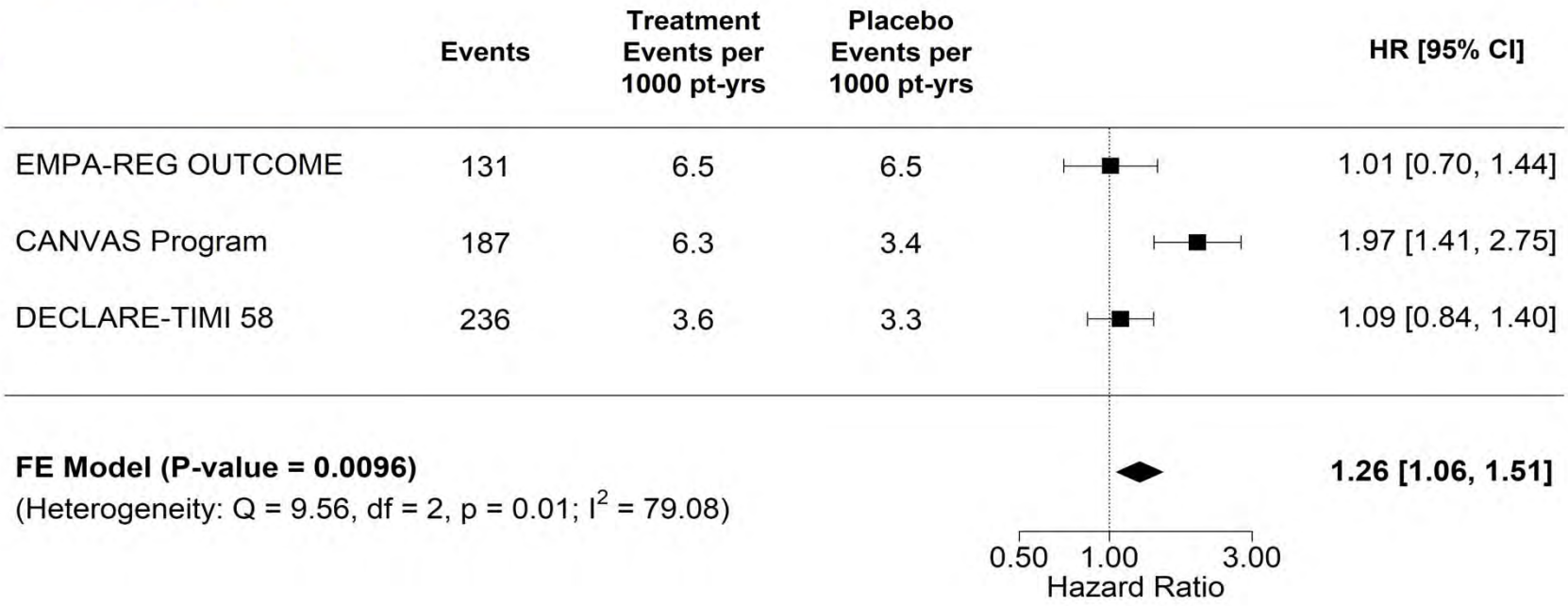
J Am Coll Cardiol 2018;72:1856–69

Side effects SGLT2 inhibitors



J Am Coll Cardiol 2018;72:1856–69

SGLT-2 CVOTs: amputations meta-analysis

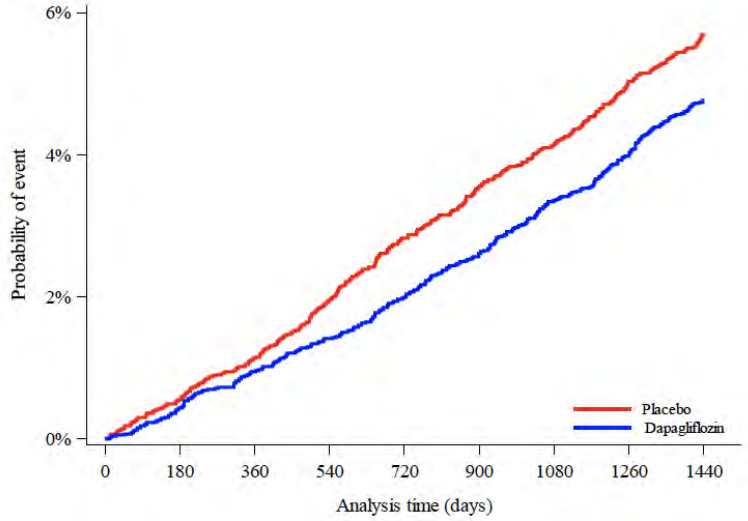


Zelniker et al. Lancet 2019

Primary Endpoints

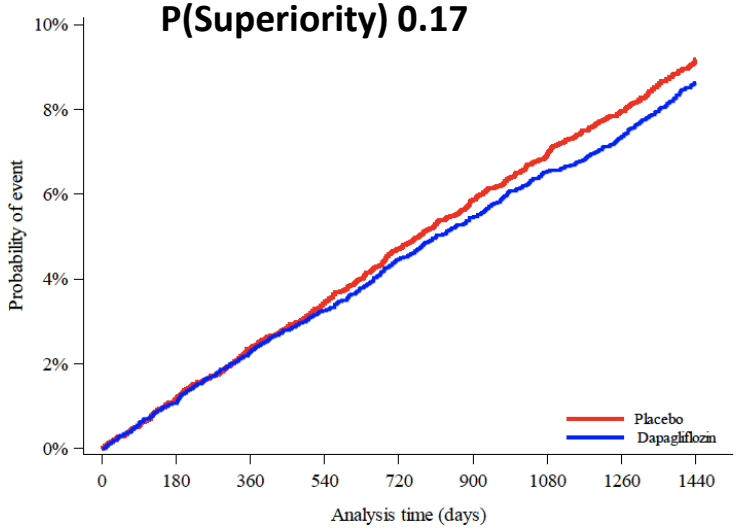
CV Death/HF hosp

4.9% vs 5.8%
HR 0.83 (0.73-0.95)
P(Superiority) 0.005



MACE

8.8% vs 9.4%
HR 0.93 (0.84-1.03)
P(Noninferiority) <0.001
P(Superiority) 0.17



Wiviott SD et al. NEJM 2018

Effects of Newer Diabetes Medications: Heart Failure

Drug Class	SAVOR TIMI-53	EXAMINE	TECOS	
DPP-4 inhibitor	✓ Increased Risk	✓ Neutral	✓ Neutral	
	LEADER	ELIXA	SUSTAIN-6	EXSCEL
GLP-1 agonist	✓ Neutral	✓ Neutral	✓ Neutral	✓ Neutral
	EMPA-REG	CANVAS	DECLARE	DAPA HF
SLGT2-Inhibitor	✓ Beneficial	✓ Beneficial	✓ Beneficial	✓ Beneficial

*HF endpoints were hospitalizations due to heart failure . DPP-4 inhibitor trials were neutral with respect to MACE (Major Adverse Cardiovascular Events: CV death, MI, stroke). No increase in the number of patients hospitalized for heart failure with sitagliptin (TECOS trial). Saxagliptin (SAVOR TIMI-53 trial), showed an increase in heart-failure events. Alogliptin (EXAMINE trial) showed a trend toward an increased risk of heart-failure events in T2DM patients

DAPA HF Trial Design

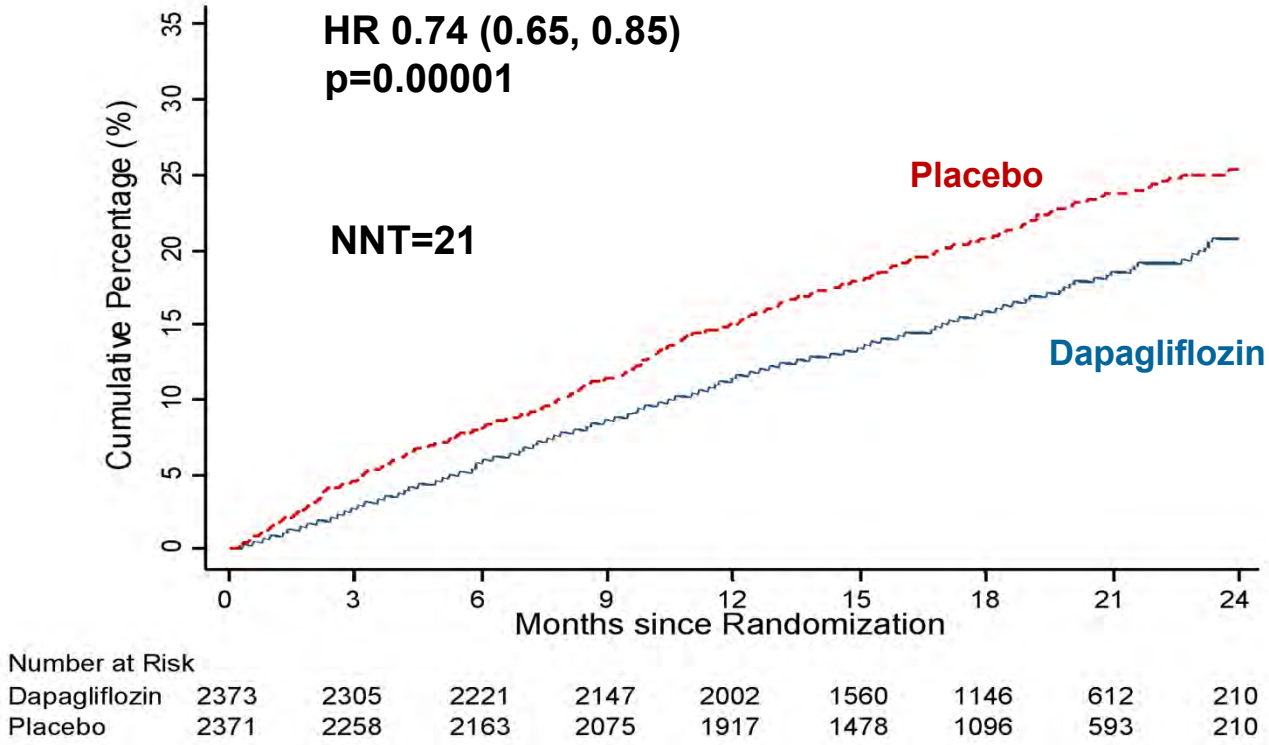
- **Key inclusion criteria:** Symptomatic HF; EF ≤40%; NT-proBNP ≥600 pg/ml (if hospitalized for HF within last 12 months ≥400 pg/mL; if atrial fibrillation/flutter ≥900 pg/mL)
- **Key exclusion criteria:** eGFR <30 ml/min/1.73 m^2; symptomatic hypotension or SBP <95 mmHg; type 1 diabetes mellitus
- **Primary endpoint:** Worsening HF event or cardiovascular death (worsening HF event = unplanned HF hospitalization or an urgent heart failure visit requiring intravenous therapy)

For full details see McMurray JJV et al Eur J Heart Fail. 2019;21:665-675

DAPAHF

Primary composite outcome

CV Death/HF hospitalization/Urgent HF visit



Number at Risk

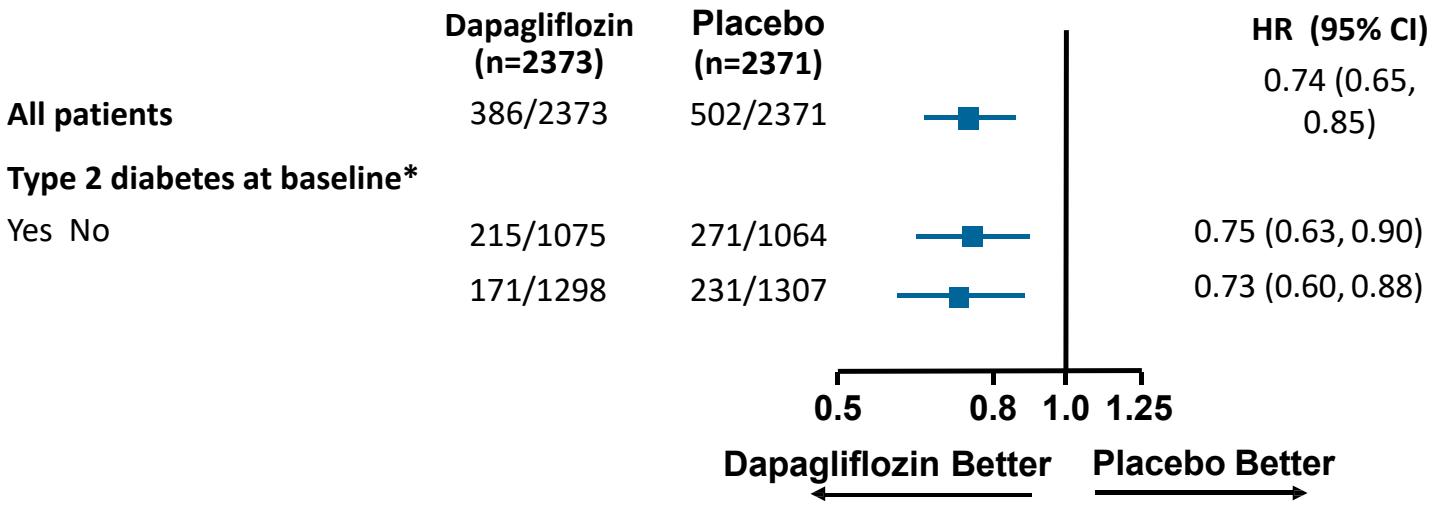
Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

n-=4,744 patients with EF ≤ .40, Creat clearance ≥ 30 ml/min

McMurray J et al. NEJM 2019

DAPAHF

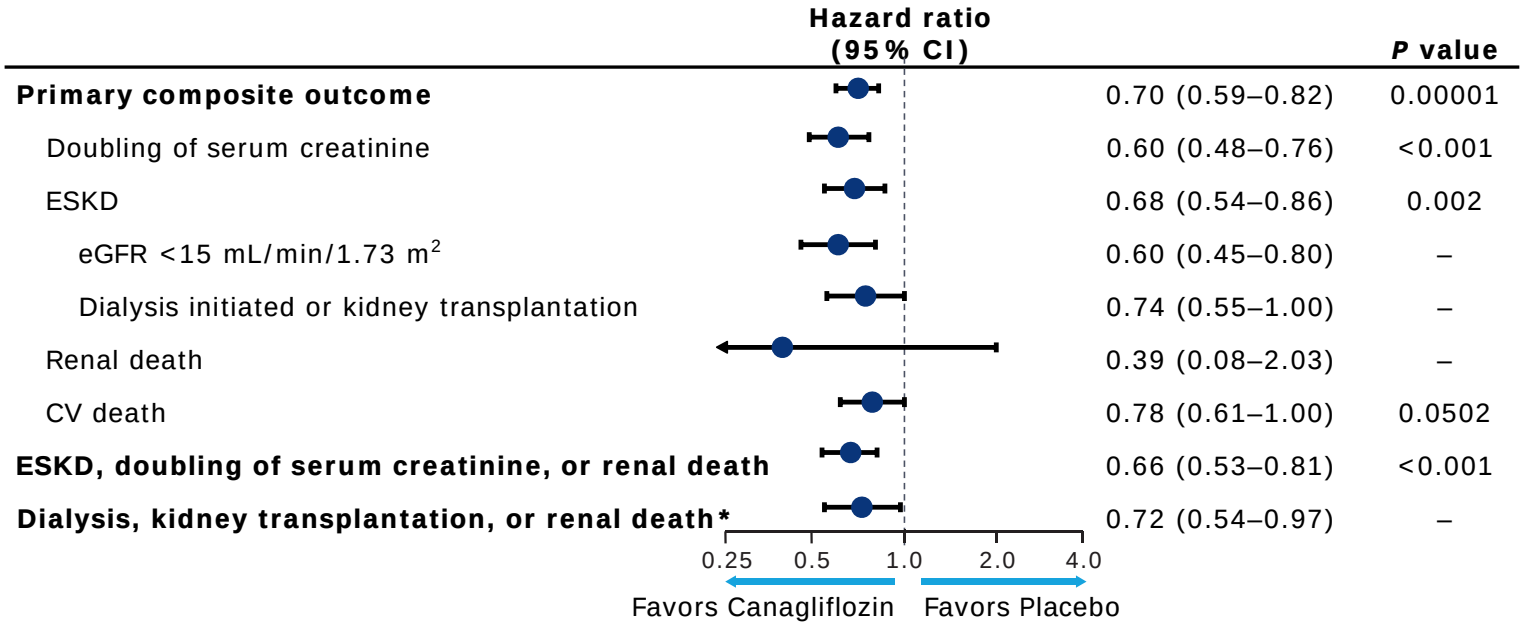
No diabetes/diabetes subgroup: Primary endpoint



*Defined as history of type 2 diabetes or HbA1c ≥6.5% at both enrollment and randomization visits.

McMurray J et al. NEJM 2019

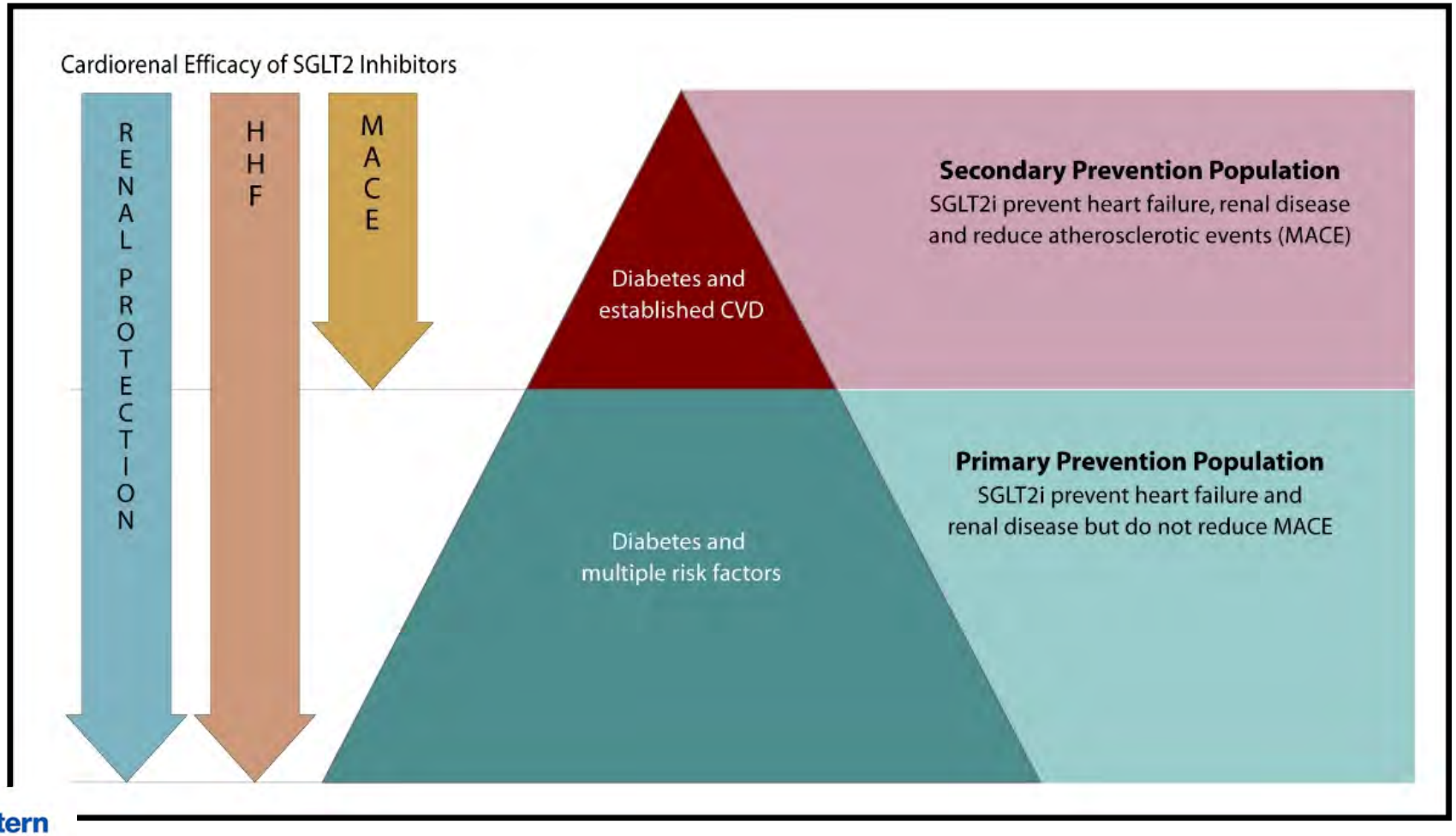
CREDENCE
Canaglifozin in pts with T2DM and creat clearance 30 – 90



Perkovic V et al. NEJM 2019

CREDENCE

SGLT-2i Effects According to Primary or Secondary Prevention

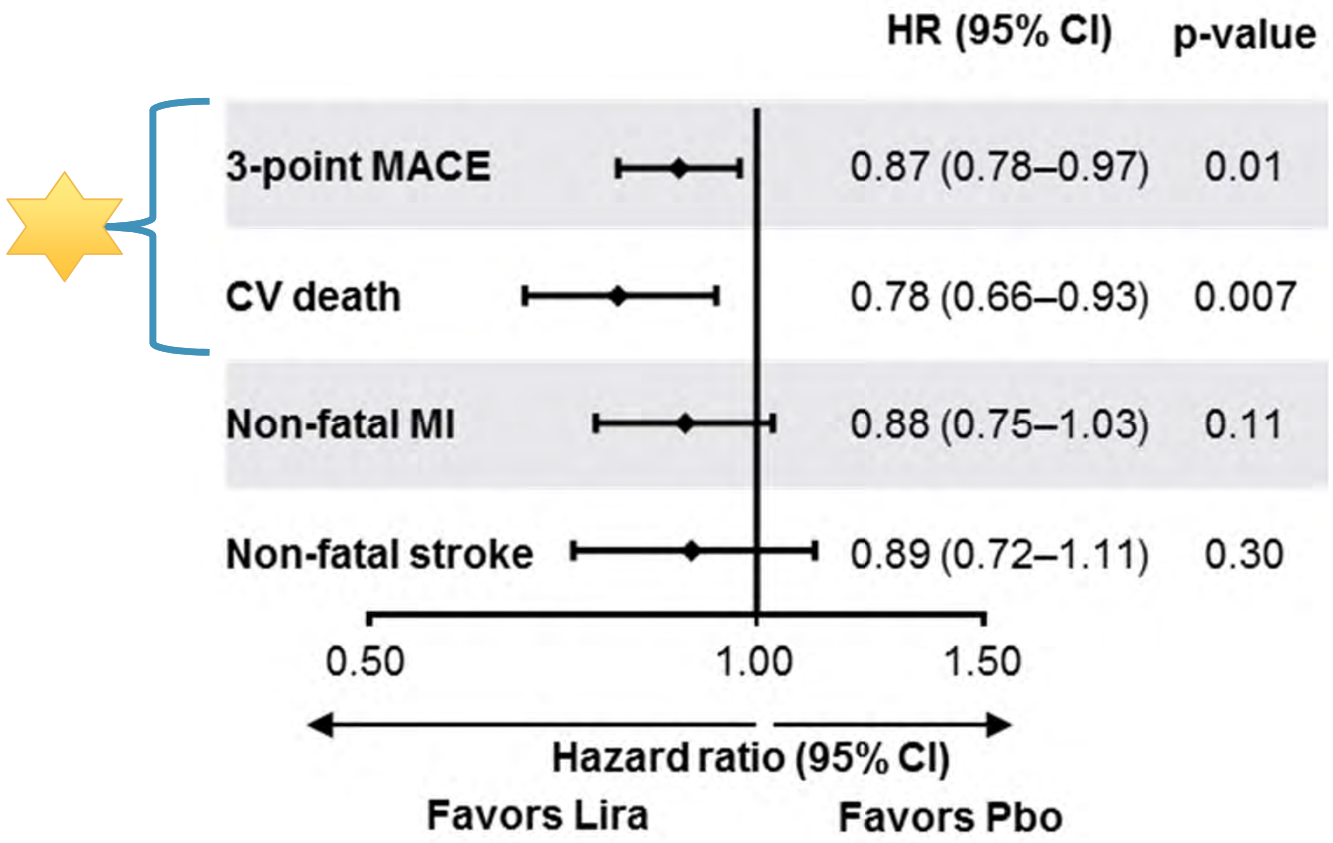


UT Southwestern Medical Center

Verma S et al. Lancet 2018; DOI 10.1016/S0140-6736(18)32824-1

GLP-1 receptor agonists

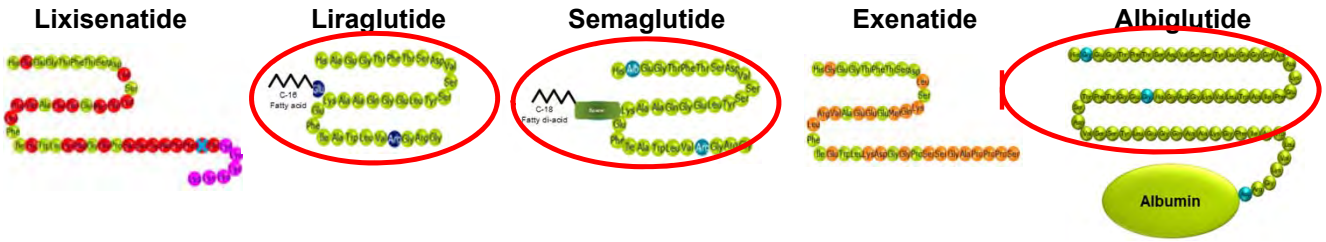
LEADER: Liraglutide – Endpoint Components



Marso SP, et al. NEJM 2016

Differences Among GLP-1 Receptor Agonists That May Have Influenced Outcomes

Drug	Lixisenatide od	Liraglutide od	Semaglutide qw	Exenatide XR qw	Albiglutide qw
Structure (sequence homology)	Exendin-4 (50%)	GLP-1 (97%)	GLP-1 (94%)	Exendin-4 (53%)	GLP-1 (97%)
In vivo EC_{50} nmol/kg)*	0.02	0.5	NA	0.01	1.4
t½	2–4 h	11.6–13 h	7 days	2 weeks	~ 5 days
Dose	20 µg	0.6–1.8 mg	0.5, 1 mg	2 mg	30, 50 mg

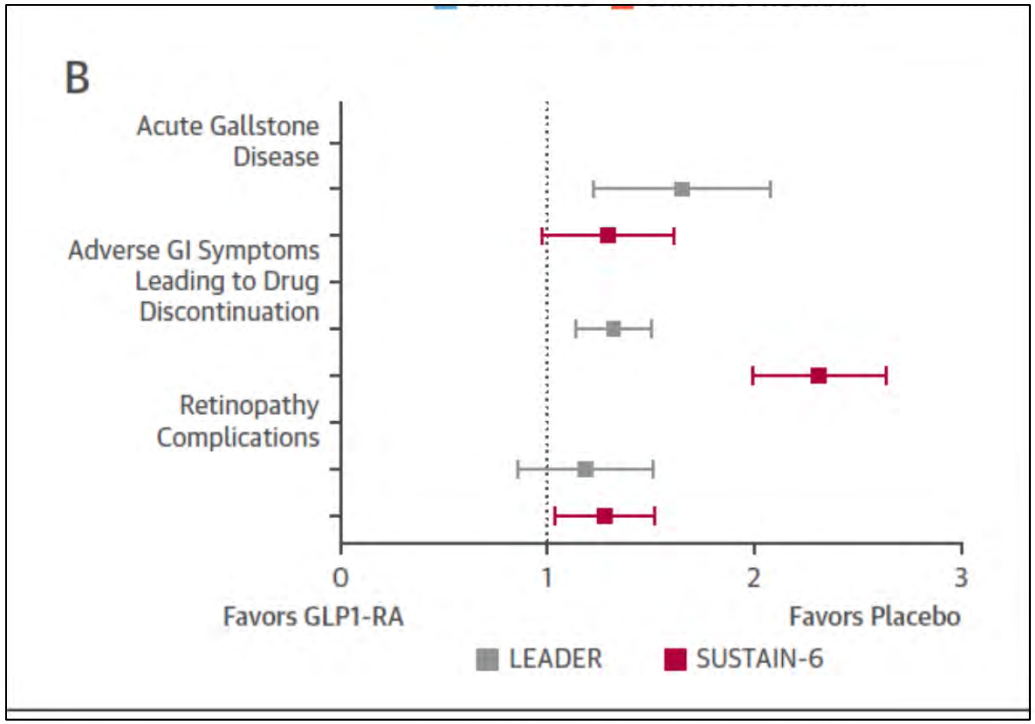


**Dose producing 50% maximal glucose AUC following OGTT in db/db mice (data on file). Exenatide EC50 values from exenatide not exenatide XR. Other data from Clin Pharmacokin 2018 (in press)*
Green circles within molecular depictions represent amino acids homologous to human GLP-1
AUC, area under curve; t1/2, terminal half-life; OGTT, oral glucose tolerance test

Harmony Outcomes

Side effects GLP-1 RA's

Less symptomatic hypoglycemia than placebo



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J Am Coll Cardiol 2018;72:1856–69

2019 ADA Guidelines

Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease, **SGLT2 inhibitors or GLP-1 receptor agonists with demonstrated cardiovascular disease benefit are recommended as part of the antihyperglycemic regimen**. **A**

ADA Standards of Medical Care in Diabetes. Diabetes Care 2019;42(S1)

ESC European Society of Cardiology

European Heart Journal (2019) **00**, 1–69
doi:10.1093/eurheartj/ehz486

ESC GUIDELINES

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD)

Cosentino F Eur Heart J 2019

2019 ESC DM/CVD Guidelines

Recommendations for glucose-lowering treatment for patients with diabetes

Recommendations	Class[a]	Level[b]
SGLT2 inhibitors		
Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce CV events.[306,308,309,311]	I	A
Empagliflozin is recommended in patients with T2DM and CVD to reduce the risk of death.[306]	I	B
GLP1-RAs		
Liraglutide, semaglutide, or dulaglutide are recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce CV events.[176,299–300,302–303]	I	A
Liraglutide is recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce the risk of death.[176]	I	B

Recommendations for the treatment of patients with diabetes to reduce heart failure risk

Recommendations	Class[a]	Level[b]
SGLT2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) are recommended to lower risk of HF hospitalization in patients with DM.[306,311,496]	I	A

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2019 ESC DM/CVD Guidelines

Recommendations for the management of patients with diabetes and acute or chronic coronary syndromes

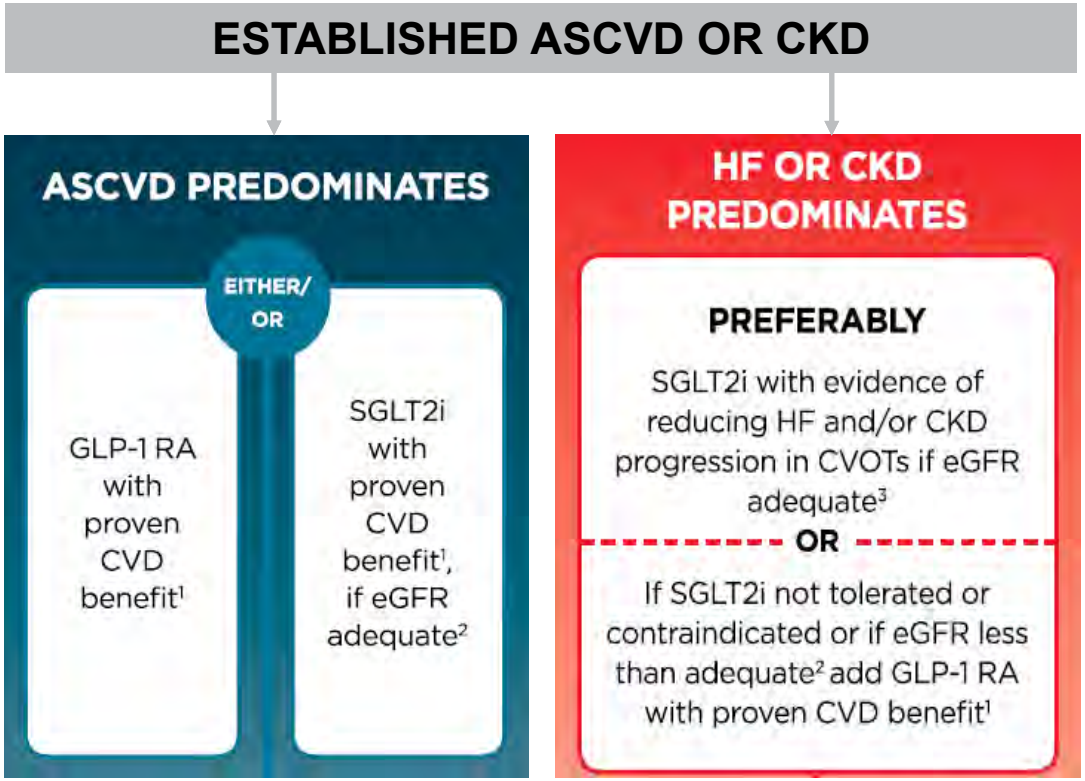
Recommendations	Class[a]	Level[b]
ACEIs or ARBs are indicated in patients with DM and CAD to reduce the risk of CV events.[326,345–347]	I	A
Statin therapy is recommended in patients with DM and CAD to reduce the risk of CV events.[211,348]	I	A
Aspirin at a dose of 75–160 mg/day is recommended as secondary prevention in patients with DM.[349]	I	A

Cosentino F Eur Heart J 2019

How do you decide whether to use a GLP-1RA or SGLT-2i?

- GLP-1RA reduce atherosclerotic events > other MACE outcomes
- SGLT-2i reduce HF events > other MACE outcomes
- SGLT-2i are oral and are somewhat “easier” to use

ADA Guidelines: *Care of the Patient with ASCVD or CKD*



Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.

Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use

Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs

American Diabetes Association. Diabetes Care. 2019;42(Suppl 1):S1-S204

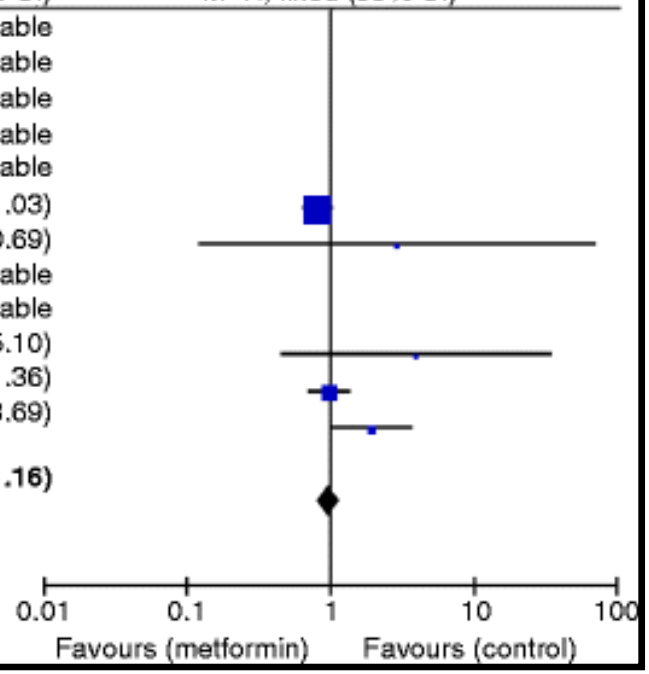
Is metformin beneficial, or just not harmful?

Is metformin helpful, or just not harmful?
Meta-analysis of CV Death

Study or subgroup	Metformin Events	Metformin Total	Control Events	Control Total	Weight	RR M–H, fixed (95% CI)
Chiasson et al (2001a) [24]	0	83	0	83		Not estimable
Chiasson et al (2001b) [24]	0	76	0	82		Not estimable
DeFronzo et al (1995a) [25]	0	143	0	146		Not estimable
DeFronzo et al (1995b) [25]	0	213	0	209		Not estimable
Hermann et al (2001) [20]	0	16	0	15		Not estimable
Holman et al (2008) [21]	81	342	120	411	62.3 %	0.81 (0.64, 1.03)
Horton et al (2000a) [26]	1	178	0	172	0.3 %	2.90 (0.12, 70.69)
Horton et al (2000b) [26]	0	135	0	134		Not estimable
Hållsten et al (2002) [19]	0	13	0	14		Not estimable
Kooy et al (2009) [22]	4	196	1	194	0.6 %	3.96 (0.45, 35.10)
Rachmani et al (2002) [27]	50	195	52	198	29.5 %	0.98 (0.70, 1.36)
UKPDS (1998) [12]	25	268	13	269	7.4 %	1.93 (1.01, 3.69)
Total (95% CI)		**1858**		**1927**	**100.0 %**	**0.97 (0.80, 1.16)**
Total events	161		186			

Heterogeneity: $\chi^2 = 8.44$, $df = 4$ ($p = 0.08$); $I^2 = 53\%$

Test for overall effect: $Z = 0.36$ ($p = 0.72$)



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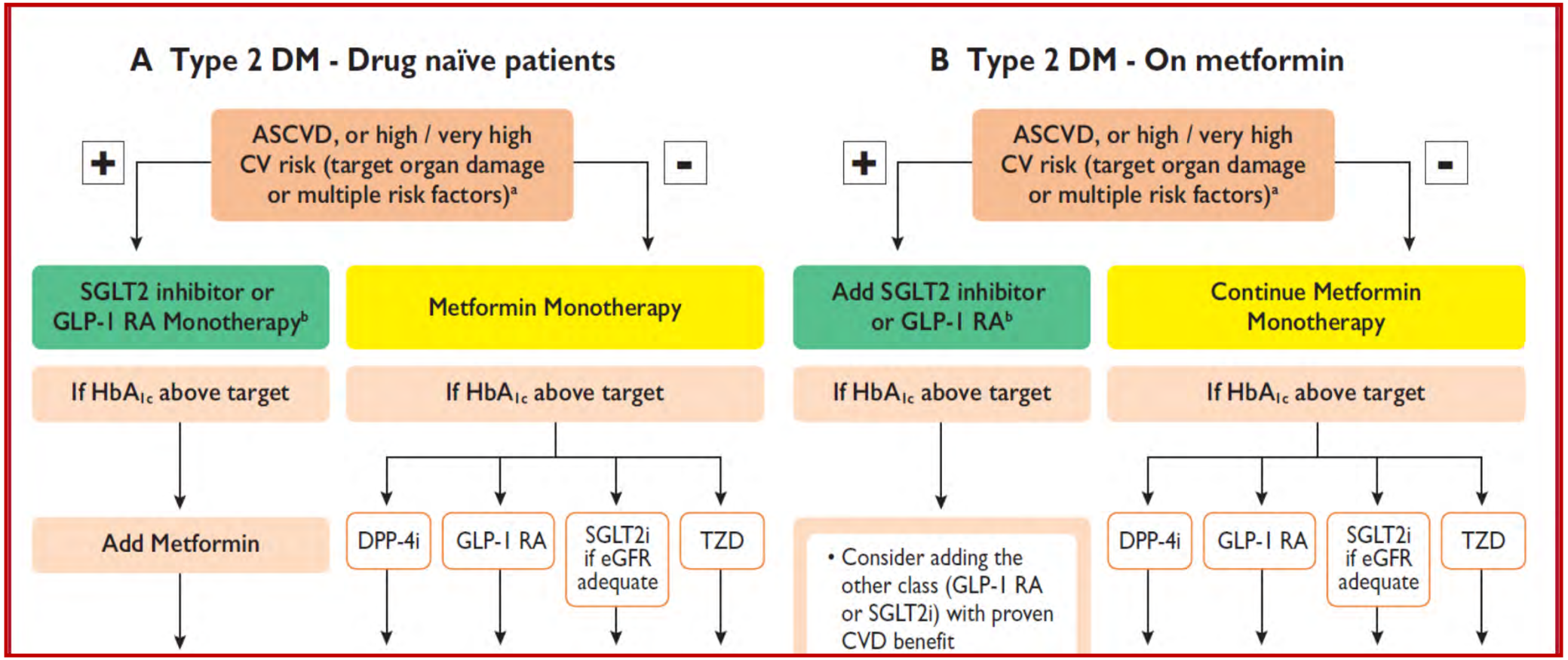
Griffin SJ et al. Diabetologia 2017;60:1620



Cosentino F Eur Heart J 2019

Now we have drugs that reduce CV events, including mortality, by 15 to 25%

But they are not being used

Barriers to Use of New Diabetes Drugs

- Therapeutic inertia
- Lack of knowledge of benefits and risks
- Concerns over side effects
  - Real
  - Perceived
- Concerns over lack of coordination with others caring for diabetes
- Cost

58 yo F with coronary disease (stent to RCA), obese and really wants to lose weight, BP 135/85 (on amlopidine), LDL 85 and TG 150 on atorva 80 mg, HbA1c 7.8 on metformin and sitagliptin (Januvia). Creatinine clearance 60 ml/m, with microalbuminuria.

In addition to lifestyle recommendations, what should you do as the cardiologist / primary care provider?

1. Add PCSK9 inhibitor
2. Add Lisinopril
3. Change sitagliptin to empagliflocin 10 mg a day
4. Change sitagliptin to liraglutide or simaglutide

PERSPECTIVE

Use of GLP-1 RAs in Cardiovascular Disease Prevention

A Practical Guide

- Start lowest dose and increase at 1-2 week intervals
- Counsel patients to expect some nausea initially that usually resolves in a week or 2 and uncommonly prohibitive
- Encourage eating small portions and stop eating when satisfied

Lingvay I and Leiter LA. Circulation 2018; 137: 2200-2202

PERSPECTIVE

Use of Sodium Glucose Cotransporter 2 Inhibitors in the Hands of Cardiologists

With Great Power Comes Great Responsibility

FRAME OF REFERENCE

- Consider altering background blood pressure medications if controlled/ low
- Consider stopping/reducing background diuretics
- If on insulin and/or sulfonylurea, consider dose reducing each of those
- Counsel re: urinary hygiene; pat dry, treat yeast infections as per routine

Cherney DZ and Udell JA. Circulation 134: 1915-1917

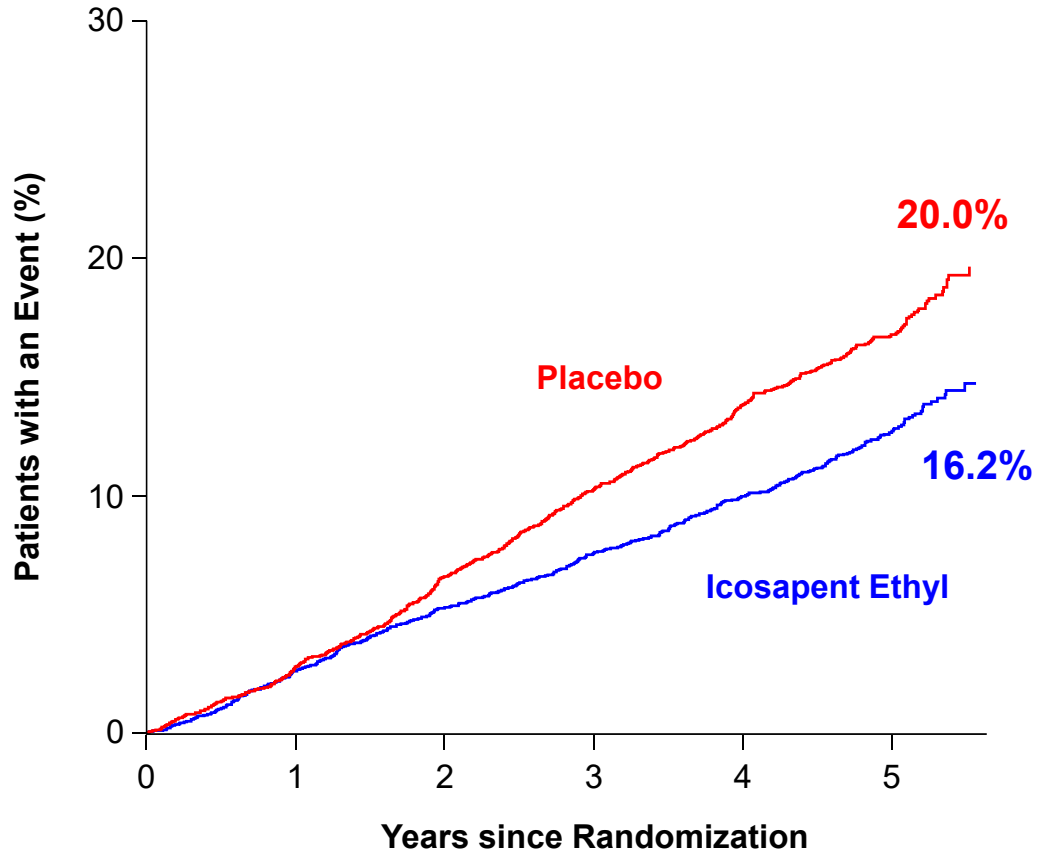
COORDINATE-Diabetes

COORDINATE-Diabetes is a randomized clinical trial to evaluate the effectiveness of implementing a clinic-level multifaceted intervention that includes establishing cardiology and diabetes care specialist partnerships, evidence-based care pathways, and measurement and feedback to improve the care of patients with T2DM and cardiovascular disease.

Fish oil provides no benefit for reducing CV risk

But how about icosapent ethyl?

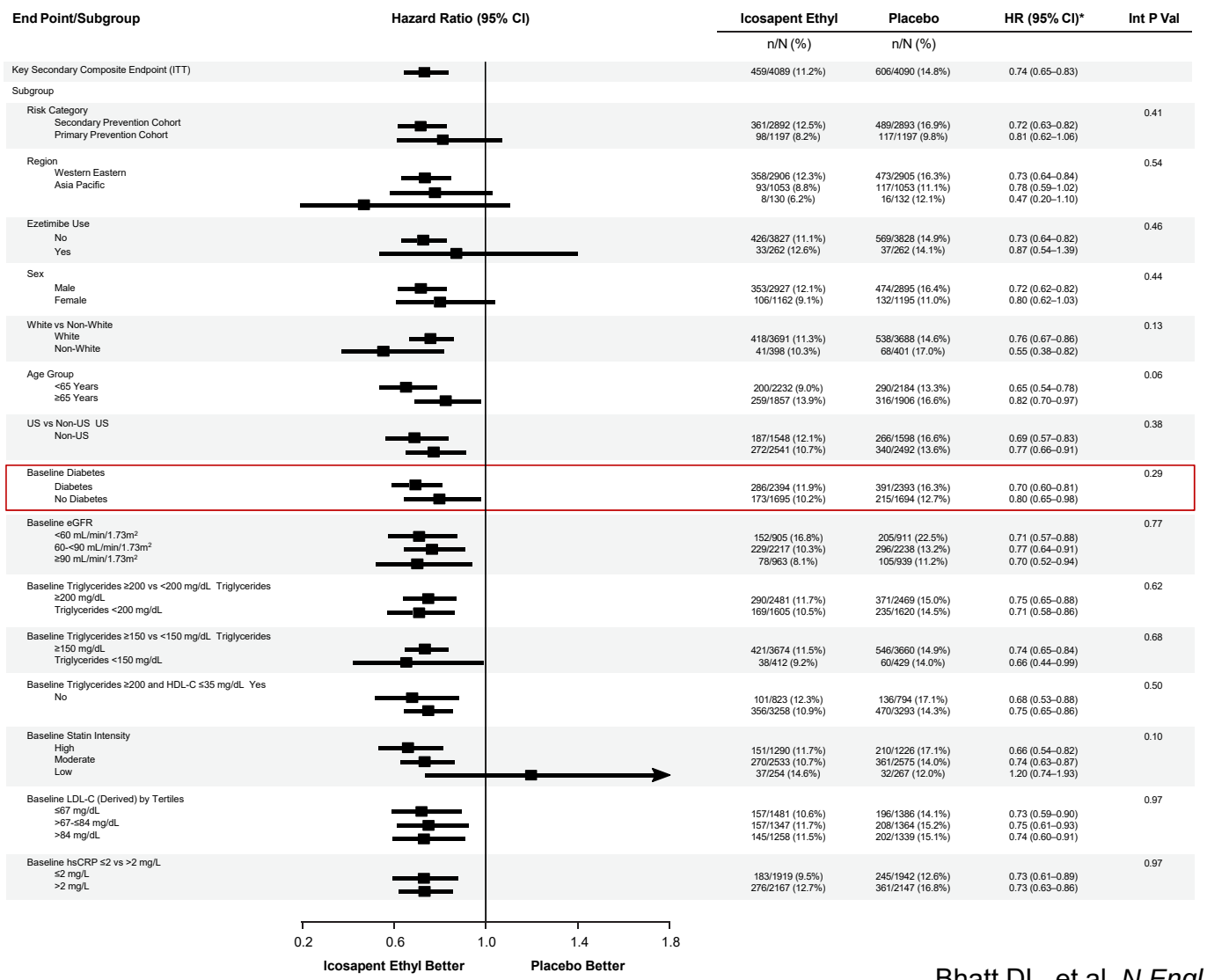
Key Secondary End Point:
CV Death, MI, Stroke



Hazard Ratio, 0.74
(95% CI, 0.65–0.83)
RRR = 26.5%
ARR = 3.6%
NNT = 28 (95% CI, 20–47)
P=0.0000006

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018. Bhatt DL. AHA 2018, Chicago.

Key Secondary End Point in Subgroups



Bhatt DL, et al. *N Engl J Med.* 2018.

64 yo M with prior anterior MI, LV EF 35, new HF (NYHA class II). BP 150/90. HbA1c 8.5, on metformin and pioglitizone. Creatinine clearance 45 ml/m.

What should you do as the cardiologist / primary care provider?

1. Recommend exercise, diet, control BP, recheck HbA1c in 2 months
2. Begin furosemide, ACE-I, beta blocker
3. Change pioglitizone to SGLT-2 inhibitor
4. Begin insulin
5. Refer to endocrinologist for diabetes management